1083-8791/05/1101-0005$30.00/0
doi:10.1016/j.bbmt.2004.09.007

Outcomes of Autologous and Allogeneic Blood or Marrow Transplantation for Mantle Cell Lymphoma

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Received August 5, 2004; accepted September 22, 2004

ABSTRACT

To evaluate high-dose therapy and autologous or allogeneic blood or marrow transplantation (BMT) for mantle cell lymphoma, patients receiving BMT for newly diagnosed or relapsed mantle cell lymphoma were identified through the registry at Johns Hopkins. The pathologic diagnostic criteria were reviewed, and details of the presentation, transplant procedure, and survival outcomes were determined. Fifty-eight patients were identified, of whom 64% underwent transplantation in first remission and 12% had primary induction failure. Nineteen patients (one third) received an allograft. Preparative regimens consisted of cyclophosphamide in combination with either busulfan or total body irradiation. On multiple regression analysis, transplantation after 1 or more relapses (hazard ratio, 2.98; $P = .02$), primary induction failure (hazard ratio, 5.39; $P = .002$), and allogeneic transplantation (hazard ratio, 3.03; $P = .007$) were associated with an inferior event-free survival (EFS). However, EFS curves were not statistically different for autologous and allogeneic BMT performed in first remission , with an estimated 3-year EFS approaching or equaling 70%. Primary induction failure and residual bone marrow involvement were the only statistically significant predictors of relapse on multiple regression analysis. At 3 years, the estimated EFS for the entire cohort after BMT was 51%, the probability of relapse was 31%, and the overall survival was 59%. The benefit of autologous or allogeneic BMT for mantle cell lymphoma is thus most apparent when transplantation is performed in first remission. Whether allogeneic BMT ultimately confers an advantage because of a graft-versus-lymphoma effect remains to be determined.

KEY WORDS

Mantle cell lymphoma • Autologous transplantation • Allogeneic transplantation

INTRODUCTION

Although at one time regarded as a low-grade non-Hodgkin lymphoma [1], mantle cell lymphoma is an aggressive disease that is generally considered incurable with conventional chemotherapy. The distinct natural history mandates that mantle cell lymphoma outcomes be studied separately from those of other lymphomas and that the diagnostic criteria be well defined in analyses of treatment outcomes. Relapse often occurs within 12 to 18 months of first-line therapy, with a typical median survival of 3 to 4 years [2,3]. Accordingly, there has been recent interest in high-dose systemic therapy with blood or marrow transplantation (BMT) for this disease. The ability of autologous BMT to prolong event-free (EFS) and overall (OS) survival in mantle cell lymphoma has been a matter of debate [4-7], and there are relatively few data on the role of fully ablative or reduced-intensity allogeneic BMT for this disease [8-12]. To further investigate the role of autologous and allogeneic BMT for mantle cell lymphoma, we report our institutional experience with these high-dose therapeutic approaches.

MATERIALS AND METHODS

Patient Selection

Through the BMT Registry at Johns Hopkins, the records of patients who received an autologous or allogeneic BMT for newly diagnosed or relapsed mantle cell lymphoma at the Johns Hopkins Oncology Center from 1980 through 2003 were screened. In

addition to the category of mantle cell lymphoma, the database was searched for potential synonyms such as centrocytic, diffuse intermediately differentiated, or diffuse poorly differentiated lymphoma [13]. The diagnosis of mantle cell lymphoma was based on a combination of morphologic and immunophenotypic (flow cytometry, tissue immunohistochemistry, or both) criteria, with or without cytogenetics [13]. In addition to basic demographic data, disease status, and vital status, study variables included presenting clinical features, type of conventional chemotherapy received, remission status before BMT, morphologic and flow cytometric bone marrow involvement before BMT, preparative regimen, stem cell source, graft manipulation, and development of graft-versus-host disease (GVHD).

The achievement of a complete or partial response to any given therapy was based on determinations of the treating physicians. Sensitive relapse was defined as a decrease in tumor size in response to the last chemotherapeutic regimen given before high-dose therapy and BMT. Rare cases of untested relapse were considered to be sensitive for the purposes of statistical analysis. Primary induction failure was defined as a lack of response to first-line treatment or disease progression within 2 months of its completion.

Permission to perform this retrospective case review was granted by the institutional review board. This analysis represents events reported through June 24, 2004.

Transplantation

Eligibility guidelines for BMT included adequate performance status (Eastern Cooperative Oncology Group performance status <2 or Karnofsky status $>70\%$); ejection fraction $\geq 45\%$; forced expiratory volume in 1 second and forced vital capacity $\geq 50\%$; bilirubin ≤ 2.0 mg/dL; creatinine ≤ 2.0 mg/dL; and absence of human immunodeficiency virus infection. Autologous BMT recipients additionally required adequate bone marrow function for harvesting or peripheral blood mobilization, with $<10\%$ residual involvement by lymphoma. Allogeneic transplantation was generally prioritized in patients ≤ 55 years of age who had an HLA-identical sibling.

Autografts were derived from bone marrow harvesting or from peripherally mobilized stem cells. The standard mobilization regimen consisted of cyclophosphamide (Cy) followed by granulocyte colony-stimulating factor, with a required yield of at least 2×10^6 $CD34^+$ cells per kilogram. Allografts in this series were derived from related donors through bone marrow harvesting and were T-cell depleted by counterflow centrifugal elutriation [14]. All but 1 transplantation used preparative regimens consisting of either Cy with total body irradiation (TBI) or busulfan (Bu) with Cy. Cy/TBI consisted of Cy (50 mg/kg/d for 4 days) followed by TBI (300 cGy/d for 4 days, with shielding of the lungs on day 3 and shielding of the liver in cases of increased transaminases). Bu/Cy consisted of Bu (1 mg/kg every 6 hours for 4 days, with dose adjustments based on pharmacokinetic calculations) followed by Cy (50 mg/kg/d for 4 days).

Cyclosporine was the first-line agent for GVHD prophylaxis after fully myeloablative allogeneic transplantation. Supportive care—including antibiotic prophylaxis, transfusions, and GVHD prophylaxis and treatment—was delivered according to standard institutional guidelines or approved clinical protocols in effect at that time.

Statistical Methods

The primary statistical end points were EFS and relapse. EFS was defined as the interval between BMT and relapse, diagnosis of myelodysplastic syndrome or acute leukemia, or death from any cause; patients without such an occurrence were censored at the date they were last known to be alive and disease free. OS was defined as the interval between BMT and the date of death or the date last known to be alive. To estimate actuarial relapse rates, patients without evidence of relapse were censored at the date of last assessment or at the date of death. Survival rates with 95% confidence intervals (CI) were estimated with the Kaplan-Meier method [15]. Nonoverlapping survival distributions were compared between groups with the log-rank statistic [16], and overlapping survival distributions were compared by using the Tarone test [17].

Analyses of prognostic factors were performed with the Cox proportional hazards model [18]. A hazard ratio (HR) >1 indicates the increase in risk of having the event relative to the reference category. The 1 recipient of a syngeneic graft was excluded from the comparison of autologous and allogeneic transplantation, and the 1 recipient of a nonmyeloablative transplant was excluded from the comparison of fully ablative preparative regimens. All P values are 2 sided. Statistical analysis was performed with Stata version 8.0 (Stata Corp., College Station, TX), with the exception of the Tarone test (SAS version 8.0; SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Fifty-eight consecutive patients who received BMT for mantle cell lymphoma were identified. Their characteristics are described in Table 1. The transplants occurred between 1993 and 2003. Other (generally earlier) cases of suspected mantle cell lymphoma were identified, but insufficient histopathologic and

Table 1. *Patient Characteristics (n = 58)*

Variable	Value
Age at BMT, y, median (range)	55 (31-72)
Months from diagnosis to BMT, median (range)	8.6 (3-62)
Male sex	48 (83%)
Initial stage, n (%)	
I	4
II	3
III*	11 (19%)
IV	40 (69%)
"B" symptoms at diagnosis (n)	6
Bone marrow involvement at diagnosis (n)	
Yes†	39
No	14
Not assessed or indeterminate	5
Presentations at diagnosis or relapse, n (%)	
Splenomegaly or splenic lesion	20 (34%)
Biopsy-proven lymphomatous polyposis	9 (16%)
Lymphocytosis	12 (21%)
First-line chemotherapy, n (%)	
CHOP ± rituximab	41 (71%)
Fludarabine, alone or in combination	10
Hyper-CVAD	2
EPOCH + rituximab	2
Other	3
Disease status at BMT, n (%)	
First remission	37 (64%)
Complete	16
Partial	21
One or more relapses	14 (24%)
Sensitive	13
Resistant	0
Untested	1
Primary induction failure	7 (12%)
Sensitive	4
Resistant	2
Untested	1
Bone marrow involvement at BMT (n)	
Yes (morphologic)	11
No	44
Flow normal	32
Flow abnormal	7
Flow not done	5
Unknown or indeterminate	3
Type of BMT, n (%)	
Autologous	38 (66%)
Allogeneic	19 (33%)
Syngeneic	1
Preparative regimen, n (%)	
Busulfan, cyclophosphamide	20 (34%)
Cyclophosphamide, TBI	37 (64%)
Fludarabine, TBI (nonmyeloablative)	1

Hyper-CVAD indicates hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.

*Initial bone marrow biopsy was not performed in 3 patients believed to have stage III disease and 2 patients with stage IV disease.

†Includes 4 cases in which bone marrow biopsy was suggestive of but not definitive for lymphomatous involvement.

confirmatory data were available on re-review to permit inclusion in this analysis.

The median age at BMT was 55 years, and most patients (88%) had at least Ann Arbor stage III disease. The incidence of bone marrow involvement, splenic involvement, gastrointestinal involvement, and lymphocytosis is described in Table 1. Most received CHOP (cyclophosphamide, hydroxydaunomycin, Oncovin [vincristine], and prednisone), with or without rituximab, as first-line therapy; fludarabine-based therapy was the next most common. Most (64%) underwent transplantation in first remission, and similar proportions of patients were in complete and partial remission before high-dose therapy (Table 1). Of the 14 patients (24%) who underwent transplantation after relapse, only 2 had more than 1 relapse. Seven patients (12%) had primary induction failure. Of all the patients in this study, only 2 had resistant relapse before high-dose therapy and BMT.

Details of the transplantation are described in Table 1. Approximately two thirds of patients received Cy/TBI, and one third received Bu/Cy. Nineteen patients (one third) received allogeneic transplants, all but 1 of which was fully myeloablative. A subset of these allogeneic transplant recipients was included in an earlier report [8]. Thirty-eight patients (two thirds) received autologous transplants, most commonly (over 80%) with peripherally mobilized, leukapheresed, cryopreserved stem cells. One patient received a syngeneic graft. Twenty-nine (76%) received peritransplantation rituximab according to protocols approved by the institutional review board. Twenty-six autografts (68%) were CD34 enriched, and a minority of autografts were purged with 4-hydroperoxycyclophosphamide [19] (n = 5) or were unmanipulated in vitro (n = 7).

Table 2. *Mortality According to Type of BMT*

Cause of Death	No. Dead
Autologous BMT	10
Early transplant related	2
Multiorgan failure	1
Multiorgan failure with VOD	1
Late transplant related	2
Acute leukemia	2
Disease progression	4
Non–cancer related	1
Unknown*	1
Allogeneic BMT	11
Early transplant related	6
Multiorgan failure	2
Diffuse alveolar damage	1
CMV pneumonitis	1
Respiratory failure and resistant disease	1
Intracranial hemorrhage	1
Late transplant related	4
Interstitial pneumonitis	1
Bronchopneumonia	1
Disseminated toxoplasmosis	1
GVHD	1
Disease progression	1

VOD indicates veno-occlusive disease; GVHD, graft-versus-host disease; CMV, cytomegalovirus.

The "early transplant" period refers to the first 100 days after BMT.

*Death occurred more than 8 years after BMT.

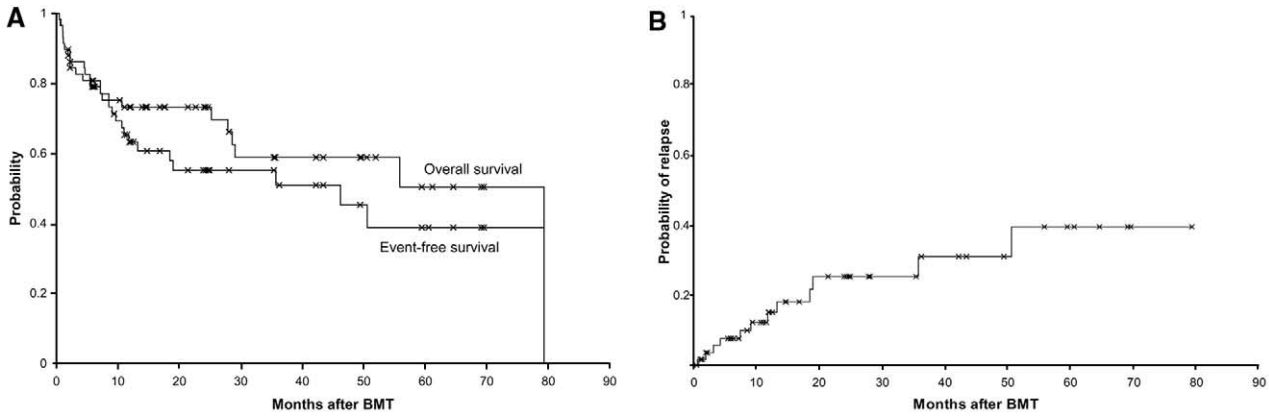

Figure 1. A, Event-free and overall survival after BMT for mantle cell lymphoma. B, Actuarial relapse rate after BMT.

Diagnostic Criteria

In 46 of the 58 cases, the presence of an 11;14 translocation was demonstrated by cyclin D1 staining (n = 43), cytogenetics, or fluorescence in situ hybridization. In 6 cases, the diagnosis was based on characteristic morphologic features and the following phenotype: $CD5^+$, $CD23^-$, $CD20^+$, and FMC-7^+. In the remaining 6 cases, the diagnosis was based on characteristic morphologic features and a partial immunophenotype. These 6 patients were diagnosed between 1993 and 1997; received either CHOP or fludarabine-based regimens as first-line therapy; and received BMT (3 autologous and 3 allogeneic) between 1997 and 2000. The EFS curves are similar with and without the latter cases (data not shown).

Survival Outcomes

By the last follow-up date, 12 relapses were documented, 8 of which occurred after autologous BMT. Four patients who received an autologous BMT were alive with relapsed disease. An additional 3 patients in the autologous group developed myelodysplastic syndrome, acute myeloid leukemia, or both; 2 have died as a result. Eight of the allogeneic transplant recipients (42%) developed GVHD. One patient in the allogeneic group was alive with relapse, which occurred more than 4 years after BMT in first partial remission. Causes of death according to the type of transplantation are listed in Table 2.

The estimated median EFS and OS of the entire cohort after BMT were 43 and 52 months, respectively (Figure 1A). The median follow-up time was 16 months for the entire cohort (range, <1 month to 79 months) and 23 months for the surviving patients. The actuarial 3-year EFS was 51% (95% CI, 35%-65%), and OS was 59% (CI, 42%-73%). The probability of relapse at 3 years was 31% (CI, 17%-51%; Figure 1B).

The EFS distributions differed significantly depending on the remission status at BMT (P = .0007; Figure 2). The EFS appeared greater in patients who underwent transplantation in first remission, compared with patients who underwent transplantation after relapse. The few patients with primary induction failure (3 of whom received autografts and 4 of whom received allografts) did poorly, although 1 of the deaths was not cancer related.

The EFS distributions for autologous and allogeneic BMT are shown in Figure 3A, and the actuarial relapse rates are shown in Figure 3B. Autologous BMT thus far has conferred a statistically significant advantage in EFS (P = .005), with an estimated median of 43 months, versus only 5.5 months for allogeneic BMT. Not unexpectedly, the early failure rate was higher in the allogeneic subgroup. However, given that the allogeneic group contained a higher proportion of patients who underwent transplantation for disease relapse, we also compared survival outcomes in patients who underwent transplantation in first partial or complete remission. It is interesting to note that for BMT in first remission, there was only 1 relapse in the allogeneic subgroup, versus 5 relapses in the autologous subgroup (figure not shown), but the significance of this is unclear given the relatively small

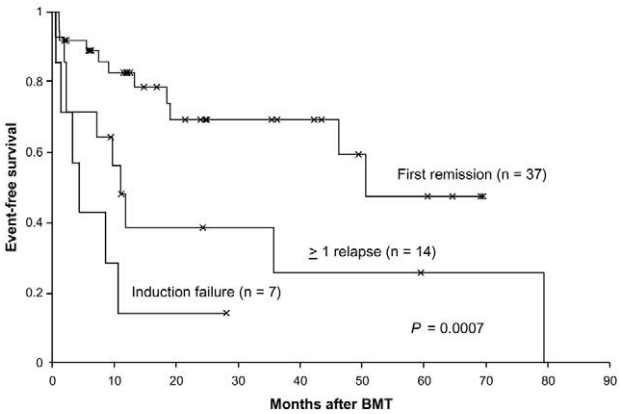

Figure 2. Event-free survival according to remission status at BMT.

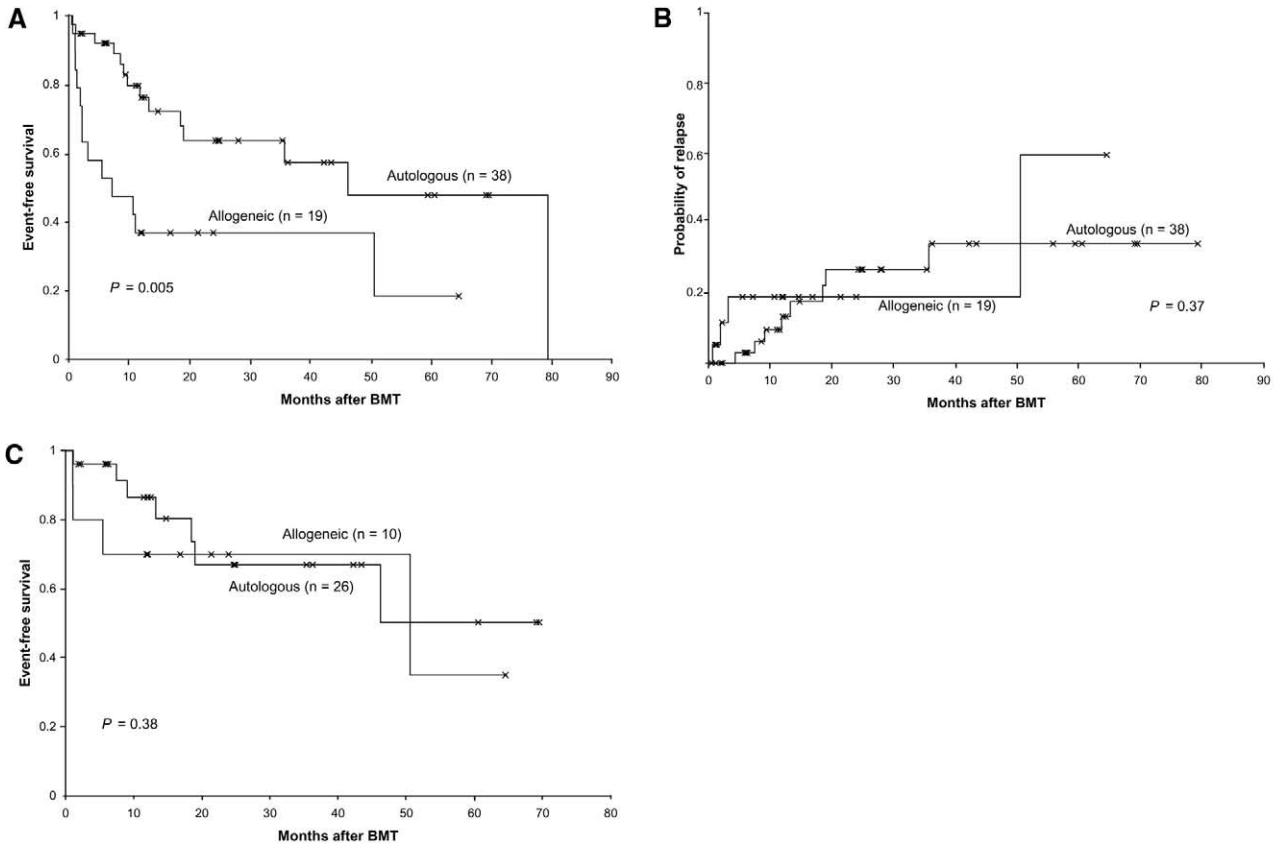

Figure 3. A, Event-free survival according to type of BMT. B, Actuarial relapse rate according to type of BMT. C, Event-free survival after autologous versus allogeneic BMT performed in first remission.

sample size. Notably, the EFS distributions were not statistically different for autologous versus allogeneic BMT performed in first remission (Figure 3C), with crossing of the survival curves and a projected 3-year EFS of approximately 70% with either approach.

Prognostic Factors

The univariate analyses for EFS and relapse risk are reported in Table 3. Allogeneic BMT and BMT performed after relapse were associated with a signif-

Table 3. *Univariate Predictors of Survival after BMT*

Variable	Event-Free Survival			Relapse		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age ≥50 y	1.82	0.62-5.33	.27	1.80	0.39-8.27	.45
Splenomegaly	1.50	0.68-3.29	.31	1.35	0.42-4.27	.62
Stage III or IV	1.47	0.44-4.93	.53	1.10	0.24-5.04	.91
PR-1*	2.08	0.55-7.88	.28	3.74	0.43-32.2	.23
BMT after ≥1 relapse†	2.63	1.09-6.37	.03	1.58	0.39-6.32	.52
Primary induction failure‡	5.91	2.11-16.5	.001	6.90	1.60-29.8	.01
Positive marrow at BMT§	1.15	0.32-4.08	.83	4.48	1.21-16.7	.03
Bu/Cy conditioning‖	0.62	0.25-1.51	.29	2.42	0.69-8.53	.17
Allogeneic BMT	2.86	1.32-6.19	.008	1.59	0.48-5.33	.45
GVHD	3.45	1.43-8.35	.006	2.11	0.46-9.82	.34

HR indicates hazard ratio; CI, confidence interval; Bu, busulfan; Cy, cyclophosphamide; PR-1, first partial remission; GVHD, graft-versus-host disease.

*Compared with BMT in first complete remission.

†Compared with BMT in first remission, excluding primary induction failure.

‡Compared with BMT in first remission.

§Morphologic and/or flow cytometric involvement.

‖Compared with cyclophosphamide/total body irradiation.

Table 4. *Multiple Regression Models for BMT Outcomes*

Variable	Event-Free Survival			Relapse		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
BMT after ≥1 relapse*	**2.98**	**1.20-7.39**	**.02**	**1.49**	**0.35-6.47**	**.59**
Primary induction failure†	**5.39**	**1.89-15.4**	**.002**	**5.26**	**1.17-23.7**	**.03**
Allogeneic BMT	**3.03**	**1.35-6.82**	**.007**	**2.05**	**0.55-7.60**	**.29**
Marrow involvement at BMT‡	**—**	**—**	**—**	**4.40**	**1.15-16.8**	**.03**

HR indicates hazard ratio; CI, confidence interval.

*Compared with BMT in first remission, excluding patients with primary induction failure.

†Compared with BMT in first remission.

‡Morphologic and/or flow cytometric involvement.

icantly inferior EFS ($P = .008$ and $P = .03$, respectively). Although the HRs for relapse exceeded 1, these variables were not statistically significant predictors of relapse. Primary induction failure also predicted a poor outcome, with a 6-fold higher risk of having an event ($P = .001$) and a 7-fold higher risk of relapse ($P = .01$). GVHD was associated with a significantly poorer EFS (likely because of its association with allogeneic BMT) but was not an independent predictor. BMT in first partial versus first complete remission and age >50 years were also associated with an inferior outcome, but the effects were not statistically significant (Table 3).

Residual morphologic and/or flow cytometric bone marrow involvement before high-dose therapy, although not a significant predictor of EFS, was associated with a >4-fold increased risk of relapse ($P = .03$). When separately assessed, residual bone marrow involvement by morphologic criteria predicted a significantly heightened relapse risk, with a trend toward higher relapse with residual flow cytometric abnormalities (data not shown). No statistically significant effect on EFS or relapse risk was seen with stage III or IV disease, "B" symptoms, splenomegaly, gastrointestinal involvement, lymphocytosis, or year of BMT as a continuous variable (data not shown).

On multiple regression analysis (Table 4), allogeneic BMT and BMT performed in the relapsed setting predicted a 3-fold higher risk of an inferior EFS. These variables were not statistically significant predictors of relapse, but they were explored because of the strength of their association with EFS. Similar to the univariate model, primary induction failure emerged as an independent predictor of inferior outcome, conferring a >5-fold greater risk of having an event ($P = .002$) or of relapsing ($P = .03$). Residual bone marrow involvement by lymphoma at the time of BMT also was an independent, significant predictor of relapse. Year of BMT was not found to be an independent predictor of EFS.

An earlier multiple regression model for EFS (before the final step-down procedure) additionally revealed a trend toward better outcomes with age <50 years (HR, 0.39; $P = .10$) and the use of Bu/Cy conditioning (HR, 0.52; $P = .17$). GVHD was also associated with a lower HR, but this did not reach statistical significance (HR, 0.47; 95% CI, 0.20-1.34; $P = .31$). A separate analysis of low-grade versus high-grade GVHD was not feasible, but the reversal of HRs on univariate (HR 3.45) and multiple regression analyses is interesting.

DISCUSSION

High-dose systemic therapy with BMT has the potential to prolong the survival of patients with mantle cell lymphoma. Our outcomes for autologous and allogeneic BMT compare favorably to those previously reported [20-22]. We had a fair number of older patients in this study, with a median age at BMT of 55 years. Furthermore, we did not exclude patients from analysis on the basis of primary induction failure or resistant relapse.

As with other non-Hodgkin lymphomas, the optimal timing of treatment intensification in mantle cell lymphoma is a matter of debate. Some have not found a significant difference in outcome according to the timing of transplantation for this disease [5]. Our data suggest that timing is an important consideration. Most patients in this series underwent transplantation in first remission, and this was associated with a superior EFS on multiple regression analysis. Others have likewise found that the benefit of BMT is most pronounced either in first remission or before multiple relapses [20,23,24]. In one of the largest series, it was found that patients who underwent transplantation in first complete remission had a significantly longer progression-free survival and OS than the rest of the cohort [21]. We did not find a statistically significant advantage to performing transplantation in first complete versus first partial remission, although there was a suggestion to that effect. However, this question is best addressed prospectively, given the potential variability in the number of debulking cycles given before BMT and in the type of first-line chemotherapy.

We had only a few patients with primary induc-

tion failure, but their outcomes were poor. In the previously described series [21], the 11 patients with refractory disease did not do worse, but others have also described poor outcomes in patients with resistant disease. In a series of allogeneic BMT for mantle cell lymphoma, for instance, patients with chemosensitive disease had an OS of 90%, compared with 44% for refractory disease [9].

There are thus far limited published data on myeloablative allogeneic BMT for mantle cell lymphoma. Two larger series have found a 2-year relapse-free survival of at least 50% [9,10], although an earlier study of allogeneic BMT (mainly or exclusively in the relapsed setting) found a 3-year EFS of 12% [25]. Not unexpectedly, allogeneic BMT was associated with a higher procedure-related mortality than autologous BMT in our analysis. However, an allogeneic approach may ultimately confer an advantage in longer-term relapse-free survival. Evidence of a graft-versus-lymphoma effect has been demonstrated in other lymphoid and myeloid malignancies, with lower relapse rates after allogeneic compared with autologous transplantation [26-28] and remissions achieved after donor lymphocyte infusion. A graft-versus-lymphoma effect in mantle cell lymphoma has been suggested by the association between remission status and development of GVHD and the conversion from molecularly detectable disease after BMT to undetectable disease over time [9]. Also of interest are the recent data on reduced-intensity approaches. Although results from an earlier report were disappointing [11], more recent data in poor-risk, heavily pretreated patients with mantle cell lymphoma seem promising [12].

Our data with up-front transplantation seem particularly promising, with estimated 3-year EFS rates for either autologous or allogeneic transplantation approaching 70%. Favorable results have similarly been reported for up-front autologous BMT in patients who respond to first-line chemotherapy, with an estimated 3-year EFS of 83% in one series [29]. Although up-front mortality is clearly higher with allogeneic transplantation, the statistical disadvantage to allogeneic transplantation may partly reflect a poorer-risk group of patients, as has been seen in other studies [28].

The curative potential of BMT remains to be defined for mantle cell lymphoma, as do the optimal timing and type of treatment intensification. The distinct natural history of this disease compared with that of low-grade lymphomas warrants dedicated study in prospective clinical trials, with clear definitions of histopathologic inclusion criteria. Our analysis, as well as some others, suggests that high-dose therapy performed early in the course of the disease may improve prognosis. If there is a benefit to treatment intensification, it is most evident early in the disease course. It remains to be seen whether such observations reflect patient selection or a true advantage to treatment intensification [6]. Longer-term follow-up and more patients are needed to determine the comparative efficacy of autologous and allogeneic BMT for this disease. There are potentially fewer transplant-related complications in patients who are less heavily pretreated [8], such that offering BMT earlier in the treatment course may confer an advantage.

More prospective data on high-dose therapy in the setting of clinical trials are needed for mantle cell lymphoma. Comparison with historical outcomes from conventional chemotherapy is potentially hindered by selection bias, variability in the efficacy of conventional chemotherapeutic regimens, and variability in histopathologic inclusion criteria. The curative potential of BMT for mantle cell lymphoma has appropriately been disputed [5]. Longer follow-up is required to determine whether the survival curve reaches a plateau, which has generally not been appreciated with trials of autologous BMT to date. Late relapses have been noted after autologous BMT for mantle cell lymphoma [29,30], and we noted a late relapse after allogeneic BMT. Given the potential for a graft-versus-lymphoma effect, fully ablative or reduced-intensity allogeneic BMT is of particular interest in this disease, alone or in combination with biologic or immunomodulatory therapies.

ACKNOWLEDGMENTS

Supported by grant nos. CA096888, CA15396, and CA09071 from the National Cancer Institute. Presented in part at the 46th Annual Meeting of the American Society of Hematology, December 4, 2004, San Diego, CA.

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